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(54) Title: TREATMENT OF DISORDERS WITH DULOXETINE

(57) Abstract

Duloxetine is the active agent in a method of alleviating several disorders, including obsessive-compulsive disorder, panic, ADHD and substance abuse.

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TREATMENT OF DISORDERS WITH DULOXETINE

The present invention belongs to the fields of medicine, psychiatric medicine and pharmaceutical chemistry, and provides several new methods of treating disorders by the administration of duloxetine.

For some years, it has been recognized that the chemistry of serotonin and norepinephrine are extremely important in neurological processes, and pharmacologists and medical researchers have been very actively studying the mechanisms of those neurotransmitters in the brain. Concomitantly, the synthesis and study of pharmaceuticals which affect serotonin and norepinephrine processes in the brain are of great interest and are also being intensively studied, both by pharmaceutical chemists and by medical researchers as well.

Duloxetine inhibits the reuptake of both serotonin and norepinephrine, and is now in clinical trials as an antidepressant drug, and also for the treatment of urinary incontinence. The present invention provides the use of duloxetine for a number of additional important purposes.

The present invention provides a method of treating or preventing a disorder in a patient having or at a heightened risk of contracting the disorder, comprising administering to the patient an effective amount of duloxetine, wherein the disorder is one of those explained below in detail.

Duloxetine is N-methyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propanamine. It is usually administered as the (+) enantiomer, and as the hydrochloride salt. It was first taught by U.S. Patent 4,956,388, which teaches the synthesis of the compound as well as its high potency as an uptake inhibitor of both serotonin and norepinephrine. The word "duloxetine" will be used here to refer to any acid addition salt or the free base of the molecule, as well as to either an enantiomer or the racemate. It is to be understood, however, that the (+) enantiomer is preferred.

The most preferred dose of duloxetine for the treatment of a given patient with any particular disorder will vary, depending on the characteristics of the patient, as all clinicians and medical doctors are aware. Factors such as other diseases from which the patient suffers, the patient's age and size, and other medications which the patient may be using will have an effect on the duloxetine dose and will be taken into account. In general, however, the daily dose of duloxetine is from about 1 to about 80 mg. A more preferred dose range is from about 5 to about 40 mg, and another preferred range is from about 5 to about 20 mg, administered once daily.

Duloxetine is orally available and presently is orally administered, in the form of a tablet or a capsule full of enteric coated granules. Oral administration in such forms is preferred in the practice of the present invention. However, other routes of administration are also practical and may be preferred in certain cases. For example, transdermal administration may be very desirable for patients who are forgetful or petulant about taking oral medicine. Sustained release formulations, oral or percutaneous, may be prepared, but are not preferred because duloxetine is quite effective when administered once daily and there is little benefit from the additional effort of preparing the sustained action product.

In general, the formulation of duloxetine for use in the present invention follows the methods used in formulating duloxetine for other purposes, and indeed methods usual in pharmaceutical science are appropriate. However, a preferred formulation of duloxetine comprises enteric pellets, or granules, of which a number are charged in a gelatin capsule.

The preferred duloxetine enteric formulation comprises a) a core consisting of duloxetine and a pharmaceutically acceptable excipient; b) an optional separating layer; c) an enteric layer comprising hydroxypropylmethylcellulose acetate succinate (HPMCAS) and a pharmaceutically acceptable excipient; d) an optional

finishing layer. The following example demonstrates the preparation of a preferred such formulation.

Example

10 mg Duloxetine base/capsule

Bill of Materials

Beads		
Sucrose - starch nonpareils,		
	20-25 mesh	60.28 mg
Duloxetine layer		
	Duloxetine	11.21
	Hydroxypropylmethylcellulose	3.74
Separating layer		
	Hydroxypropylmethylcellulose	2.51
	Sucrose	5.00
	Talc, 500 mesh	10.03
Enteric layer		
	HPMCAS, LF grade, Shin-Etsu Chemical Co., Tokyo, Japan	25.05
	Triethyl citrate	5.00
	Talc, 500 mesh	7.52
Finishing layer		
	Hydroxypropylmethylcellulose	8.44
	Titanium dioxide	2.81
	Talc	Trace
		141.60 mg

The duloxetine layer was built up by suspending duloxetine in a 4% w/w solution of the hydroxypropylmethylcellulose in water, and milling the suspension with a CoBall Mill (Fryma Mashinen AG, Rheinfelden, Switzerland) model MS-12. A fluid bed dryer with a Wurster column was used to make this product, at a batch size of 1.0 kg. The separating layer was added from a 4% w/w solution of the hydroxypropylmethylcellulose in water, in which the sucrose was also dissolved.

In order to prepare the enteric coating suspension, purified water was cooled to 10°C and the polysorbate,

triethyl citrate and silicone emulsion were added and dispersed or dissolved. Then the HPMCAS and talc were added and agitated until homogeneity was obtained, and the HPMCAS was fully neutralized by addition of ammonium hydroxide until solution of the polymer was complete. To this suspension, a carboxymethylcellulose aqueous solution, 0.5% w/w, was added and blended thoroughly. The enteric suspension was maintained at 20°C during the coating process. The enteric suspension was then added to the partially completed pellets in the Wurster column at a spray rate of about 15 ml/min, holding the temperature of the inlet air at about 50°C. The product was dried in the Wurster at 50°C when the enteric suspension had been fully added, and then dried on trays for 3 hours in a dry house at 60°C. A finishing layer was then applied which consisted of a 4.5% w/w/ hydroxypropylmethyl-cellulose solution containing titanium dioxide and propylene glycol as plasticizer. The pellets were completely dried in the fluid bed dryer and then were then filled in size 3 gelatin capsules.

The patient to be benefited by practice of the present invention is a patient having one or more of the disorders discussed in detail below, or who is at a heightened risk of contracting such disorder. Diagnosis of these disorders, or the identification of a patient at risk of one or more of them, is to be made by a physician or psychiatrist. It is presently believed that duloxetine's potency in inhibiting the uptake of serotonin and norepinephrine is the mechanism by which it benefits such patients, by alleviating the effects of the disorder from which the patient suffers, or even eliminating the disorder completely.

A patient with a heightened risk of contracting one of the present disorders is a patient, in the present contemplation, who is more likely than is a normal person to fall victim to that disorder. The patient may have suffered from the disorder in the past, and be at risk of a relapse, or may exhibit symptoms which demonstrate to the physician or

psychiatrist that the patient is under an abnormal risk of developing the disorder in its full form.

The disorders which are treated or prevented in the practice of the present invention may be described as follows.

bulimia nervosa
obsessive-compulsive disorder
premenstrual dysphoric disorder
substance abuse
substance dependence
panic disorder
panic attack
agoraphobia
post-traumatic stress disorder
neuropathic pain
dementia of Alzheimer's type
migraine
social phobia
attention deficit hyperactivity disorder
disruptive behavior disorder
intermittent explosive disorder
borderline personality disorder
chronic fatigue syndrome
premature ejaculation
depression and behavioral problems associated with head injury, mental retardation or stroke.

Most of the disorders discussed here are described and categorized in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, published by the American Psychiatric Association, 1994. In the discussion below, the DSM codes for the disorders will be given where appropriate.

Bulimia nervosa, DSM 307.51, is characterized by uncontrollable binge eating, followed by self-induced purging, usually vomiting. Its prevalence is as high as 1%-3% among adolescent and young adult females. The disorder is

well characterized and recognized by the health professions. The essential features of it are binge eating and inappropriate compensatory methods to prevent weight gain. Further, individuals with the disorder are excessively influenced by body shape and weight.

Obsessive-compulsive disorder, DSM 300.3, is characterized by recurrent obsessions or compulsions which are severe enough to be time consuming or cause distress or impairment of the patient's life. Obsessions are persistent ideas, thoughts, impulses or images which are recognized by the patient to be intrusive and inappropriate and cause anxiety or distress. The individual senses that the obsession is alien, not under control and not the kind of thought that the patient would expect to have. Common obsessions include repeated thoughts about contamination, repeated doubts, a need to arrange things in a particular order, aggressive or horrific impulses and sexual imagery. Compulsions are repetitive behaviors, such as hand washing, or mental acts, such as counting or repeating words silently, the goal of which is to prevent or reduce anxiety or distress. By definition, compulsions are either clearly excessive or not realistically connected with that which they are designed to neutralize or prevent. Obsessive-compulsive disorder is rather common, with an estimated lifetime prevalence of 2.5%.

Substance abuse and substance dependence, very well known in most societies at present, come about when the patient becomes addicted or habituated to the improper use of a drug or other substance. Several different varieties of substance abuse and dependence will be discussed in detail below. It will be understood that substance abuse or dependence often results in additional disorders, including intoxication, withdrawal symptoms, delirium, psychotic disorders, hallucinations, mood disorders, anxiety disorders, sexual dysfunctions, or sleep disorders. Recognized substance abuse and substance dependence disorders which are part of the present invention include the following:

amphetamine dependence, DSM 304.40
amphetamine abuse, DSM 305.70
cannabis dependence, DSM 304.30
cannabis abuse, DSM 305.20
cocaine dependence, DSM 304.20
cocaine abuse, DSM 305.60
hallucinogen dependence, DSM 304.50
hallucinogen abuse, DSM 305.30
inhalant dependence, DSM 304.60
inhalant abuse, DSM 305.90
nicotine dependence, DSM 305.10
opioid dependence, DSM 304.00
opioid abuse, DSM 305.50
phencyclidine dependence, DSM 304.90
phencyclidine abuse, DSM 305.90
sedative, hypnotic or anxiolytic dependence, DSM 304.10
sedative, hypnotic or anxiolytic abuse, DSM 305.40
polysubstance dependence, DSM 304.80

The prevalence and deleterious effects of substance dependence and substance abuse are almost too well known to discuss. The disorders are characterized, in general, by a compulsion to use the substance in question in order to obtain its effects, regardless of the ill-effects of the substance or the difficulty, expense or danger of obtaining it. Some substances of abuse, such as cannabis and cocaine, have run through entire sections of society and have damaged or ruined untold numbers of lives. The importance of duloxetine's ability to relieve such disorders in accordance with the present invention is obviously of great significance.

Panic attack, panic disorder and agoraphobia, categorized as DSM 300.01, 300.21 and 300.22, affect between 1.5% and 3.5% of the population. The disorders are characterized by irrational sense of imminent danger or doom,

an urge to escape, or a fear of being in a situation from which escape might be difficult. The patient exhibits symptoms such as palpitations, accelerated heart rate, sweating, sensations of shortness of breath, chest pain, nausea, dizziness, fear of dying, and the like, and may have such attacks very frequently.

Social phobia, DSM 300.23, produces a marked and persistent fear of social or performance situations in which embarrassment may occur. Exposure to such a situation may result in a panic attack, or other anxious response. Most often, patients with the disorder simply avoid situations of the type which they dread, producing an obvious dislocation in the patient's life. The prevalence of social phobia has been reported as from 3% to 13%, on a lifetime basis.

Post-traumatic stress disorder, DSM 309.81, afflicts patients following exposure to a traumatic stress involving personal experience of an event involving actual or threatened death of injury. Such traumatic events include experiences such as military combat, personal assault, kidnapping, terrorist attack, torture, natural or man-made disasters, severe accidents, or being diagnosed with a dreaded illness. Learning about such events occurring to others, particularly a family member or close friend, also may produce the disorder. Triggering events which symbolize the traumatic event, such as an anniversary, may recreate the stress and bring on the disorder long after the event is passed. Patients strive to avoid stimuli associated with the trauma, even to the point of amnesia or reduced responsiveness to other people in general. Prevalence of post-traumatic stress disorder has been reported at from 1% to as much as 14%, and has been reported at 50% and more in studies of individuals who are at risk of the disorder.

Dementia of the Alzheimer's type, DSM 290.11, 290.12, 290.13, 290.10, 290.3, 290.20, 290.21 and 290.0, affects between 2% and 4% of the population over 65 years old. The prevalence increases with age, particularly after 75 years of age, and is associated with Alzheimer's disease. In most

patients, brain atrophy or deterioration is present, and is associated with the dementia.

Attention deficit hyperactivity disorder, DSM 314.01 and 314.00, is primarily recognized as a disorder of children, but may well be found in adults as well. It is characterized by symptoms such as lack of attention, impulsivity, and excessive activity, resulting in high expenditure of effort accompanied with a low degree of accomplishment. Patients have difficulty or find it impossible to give attention to details, cannot sustain attention in tasks or even play, and make careless mistakes. They fail to listen to or follow through on instructions, lose things, and are easily distracted by extraneous events. The difficulty of such patients in carrying out useful lives is obvious from the mere recital of the symptoms.

Disruptive behavior disorder, DSM 312.9, is a condition characterized by aggressive, destructive, deceitful and defiant activity.

Intermittent explosive disorder, DSM 312.34, is characterized by episodes of failure to resist aggressive impulses, resulting in assault or destruction of property. The degree of aggressiveness expressed during episodes of this disorder is grossly disproportionate to any provocation or triggering stress. The Southeastern Asian condition of amok is an episode of this disorder, cases of which have been reported in Canada and the United States as well.

Borderline personality disorder, DSM 301.83, is marked by a pervasive pattern of instability of interpersonal relationships and self-image, and marked impulsivity which begins by early adulthood. Patients have a pattern of unstable and intense relationships, very quickly developing a very close relationship and then quickly devaluing the other person. Patients may gamble, spend irresponsibly, binge eat, abuse substances, engage in unsafe sex or drive recklessly. Patients often display recurrent suicidal behavior or self-injurious behavior. The prevalence is estimated to be about 2% of the population.

Neuropathic pain, as distinct from other varieties of pain, emanates specifically from a neurologic source, as from a nerve which is unnaturally stressed, compressed or otherwise injured, it does not include pain emanating from an injury or inflammation of bone, muscle or other tissue.

Migraine is well-known as a headache, particularly a very severe headache, which occurs repetitively in patients subject to the condition. It has been treated with partial success with vasoconstrictors but no treatment of migraine in the prior art is reliably successful.

Premature ejaculation, DSM 302.75, is characterized by the inability of a male to delay orgasm as long as is desired.

Depression and behavioral problems associated with head injury, mental retardation or stroke are treated in the exercise of the present invention. Such depression and behavioral problems are distinct from the usual such disorders, because of their origin. Depression, of course, of the general type is quite prevalent and is now well-known, being well treated with pharmaceuticals such as, for example, fluoxetine.

Chronic fatigue syndrome is a condition which has been variously described and diagnosed. It is sometimes categorized as a low-grade viral infection, particularly caused by the Epstein-Barr virus. Since that virus is very widely found in the population, however, the diagnosis is problematic. An alternative characterization of chronic fatigue syndrome is a physical-psychological disorder of the depression type, characterized primarily by lack of energy and listlessness.

Premenstrual dysphoric disorder is characterized by symptoms such as feelings of sadness, hopelessness or self-deprecation; anxiety or tenseness; tearfulness and lability of mood; persistent irritability and anger; decreased interest in usual activities or withdrawal from relationships; difficulty concentrating and the like. It is not classified formally by DSM but is discussed in detail

there. The pattern of symptoms occurs in most cycles, frequently beginning the week prior to menses. Frequently, the disorder markedly interferes with the patient's life in all respects during the attack of the disorder. The prevalence of the disorder in its most profound form has been estimated at 3%-5%, but there has been little systematic study on the course and stability of the condition.

Claims

1. Duloxetine, for use for treating or preventing a disorder in a patient having or at a heightened risk of contracting the disorder, wherein the disorder is bulimia nervosa, obsessive-compulsive disorder, premenstrual dysphoric disorder, substance abuse, substance dependence, panic disorder, panic attack, agoraphobia, post-traumatic stress disorder, neuropathic pain, dementia of Alzheimer's type, migraine, social phobia, attention deficit hyperactivity disorder, disruptive behavior disorder, intermittent explosive disorder, borderline personality disorder, chronic fatigue syndrome, premature ejaculation, or depression and behavioral problems associated with head injury, mental retardation or stroke.

2. A use of Claim 1 wherein the disorder is bulimia nervosa, obsessive-compulsive disorder, or premenstrual dysphoric disorder.

3. A use of Claim 1 wherein the disorder is substance abuse or substance dependence, amphetamine dependence or amphetamine abuse, cannabis dependence or cannabis abuse, cocaine dependence or cocaine abuse, hallucinogen dependence or hallucinogen abuse, inhalant dependence or inhalant abuse, nicotine dependence, opioid dependence or opioid abuse, phencyclidine dependence or phencyclidine abuse, sedative, hypnotic or anxiolytic dependence or sedative, hypnotic or anxiolytic abuse, or polysubstance dependence.

4. A use of Claim 1 wherein the disorder is panic disorder, panic attack or agoraphobia, post-traumatic stress disorder, neuropathic pain or migraine, or dementia of Alzheimer's type.

5. A use of Claim 1 wherein the disorder is social phobia, attention deficit hyperactivity disorder, or disruptive behavior disorder or intermittent explosive disorder.

6. A use of Claim 1 wherein the disorder is borderline personality disorder, chronic fatigue syndrome,

premature ejaculation, or depression and behavior problems associated with head injury, mental retardation or stroke.

7. The use of duloxetine for the manufacture of a medicament for treating or preventing a disorder in a patient having or at a heightened risk of contracting the disorder, wherein the disorder is as claimed in any one of Claims 1 through 6.

8. A pharmaceutical composition for treating or preventing a disorder in a patient having or at a heightened risk of contracting the disorder, comprising duloxetine as the active ingredient, associated with one or more pharmaceutically acceptable carriers, wherein the disorder is as claimed in any one of Claims 1 through 6.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER

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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/438

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPIDS, BIOSIS,HCAPLUS, EMBASE- Search terms:Duloxetine and various psychological or psychiatric disorders

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ZA, A, 93/0694 (ELI LILLY AND COMPANY) 28 July 1993, see entire document.	1-8

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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